II. REMARKS

Claims 1, 7-9, 12-14, 18, 22-26, and 30-36 are pending. A marked version of claims 1, 9, 18, 26 and 34, showing the amendments, is attached as Exhibit A.

A. Regarding the Amendments

Claims 1, 9, 18, 26 and 34 have been amended to more clearly indicate that a polynucleotide useful in a method of the invention, comprises an operatively linked expression regulatory element. The amendment is supported, for example, at page 24, second full paragraph, and, therefore, does not add new matter.

It is submitted that the amendment does not require a new search or consideration because it was clear from the claims as previously pending that the polynucleotides were to be expressed, and because the matter has already been considered as indicated by the Examiner noting that the claims did not recite such a regulatory element. The amendment was not made previously because the rejection is newly made in the present Office Action (see, also, Section B, below). It is submitted that the amendments place the claims in condition for allowance, or in better condition for appeal. As such, it is respectfully requested that the amendments be entered.

B. Removal of Finality of the Office Action

The claimed methods are rejected, in part, because the polynucleotides to be used in a method of the invention, do not include "any expression regulatory elements" and the "specification does not provide any guidance for expressing the recited polynucleotides in the absence of expression regulatory elements (see Office Action, paragraph bridging pages 4-5). Applicants submit that this is a new ground of rejection that could have been made in the previous Office Action and was not necessitated by the previous amendment of the claims. As such, it is submitted that the present Office Action should not have been made final. Accordingly, it is respectfully requested that the Finality of the present Office Action be removed, and that, if the claims are not found to be in condition for allowance, that a further

C. Rejection under 35 U.S.C. § 112, first paragraph, (enablement)

The rejection of claims 1, 7-9, 12-14, 18, 22-26, and 30-36 as allegedly lacking enablement, is respectfully traversed.

Applicants respectfully disagree that the specification does not teach one skilled in the art how to make and/or use the invention commensurate in scope with the claims. It is well-established that the claims of a patent application are presumptively enabled when the application is filed. Thus, the burden of demonstrating that the entire breadth and scope of the claims is not enabled falls on the Examiner. In the present case, the Examiner continues to make the same broad based rejections despite the previous amendments to the claims and the evidence of record. Accordingly, for the following reasons, and for the reasons of record (some of which are summarized below), it is respectfully submitted that the Examiner has not met the burden of demonstrating non-enablement of the claimed methods.

As an initial matter, it is noted, as discussed above, the claims are rejected in part as lacking enablement for expression of a polynucleotide as recited in the claims, wherein the polynucleotide is not operatively linked to expression regulatory elements. The claims have been amended to address this matter and, therefore, it is submitted that this issue is moot.

The Examiner sets forth three premises that form the basis for the remaining grounds supporting the alleged lack of enablement: 1) the specification allegedly provides no evidence that the recited polynucleotides produce a polypeptide *in vivo*; 2) the specification allegedly provides no nexus between a lack of expression of polypeptides encoded by the recited polynucleotides and a malignant hyperproliferative state; and 3) the specification does not enable methods of *in vivo* gene therapy. Each of these premises is addressed below.

First, the specification discloses that 5'ALT/p15^{INK4B} (hereinafter 5'ALT/p15) and

and paragraph bridging pates 50-5[illegible], and *in vitro* of 5'ALT p16 (Example 4, page 5[illegible] Based on

such information, Applicants submit that one skilled in the art reasonably would have known that 5'ALT/p15 and 5'ALT/p16 polypeptides can be expressed in a cell from such encoding polynucleotides. Further, the specification discloses that alternative splicing is well known and, for example, is involved in sex determination in *Drosophila* and in many examples of tissue-specific gene expression. Thus, expression of polypeptides encoded by alternatively spliced RNA molecules is well known. While, as the Examiner appears to suggest, it may be that the transcripts are not in fact translated in cells *in vivo*, the Examiner has not provided any objective in support of this position. Specifically, the Examiner has not provided any evidence of other transcripts that are expressed in a cell, and can be translated *in vitro,* but that are not in fact translated *in vivo.* Thus, in view of the present disclosure, as well as of knowledge in the art regarding expression polypeptides from alternatively spliced RNA transcripts, and absent any objective evidence to the contrary, it is submitted that the Examiner has no basis for maintaining this ground of rejection.

Second, the specification discloses 1) that 5'ALT/p15 and 5'ALT/p16 transcripts were identified in 8 tumor cell lines (paragraph bridging pages 56-57); 2) that these transcripts are alternatively spliced transcripts of $p15^{INK4B}$ and 5'ALT/$p16^{INK4A}$, which are tumor suppressor genes that are often deleted in cancer and, as disclosed in the specification for p16, can be hypermethylated in different types of cancer cells (see, for example, page 73, first paragraph; and page 75, second full paragraph); and 3) that a cell proliferative disorder such as a cancer can be treated be expressing the 5'ALT/p15 or 5'ALT/p16 polypeptide in cells associated with the disorder (paragraph bridging pages 29-30). Further, the Liggett, et. al. reference, which is of record in this case and includes work of one of the co-inventors of the subject application, provides confirmatory evidence that, as disclosed in the specification, introduction of a polynucleotide encoding p16β, which is the 5'ALT/p16 polypeptide of the present invention (see Liggett et al., page 4119, right column, first full paragraph, and Refs. 12 and 13 cited therein), and expression of the p16β polypeptide in head and neck squamous cell carcinoma (HNSCC)

there is a clear nexus between the lack of expression of a 5'ALT/p16 and the malignant state because expression of 5'ALT/p16 (p16β) inhibited the growth of malignant cells, as disclosed in the specification and confirmed by Liggett et al., and that in the absence of evidence to the contrary, there is no reason to believe that there is a similar nexus between 5'ALT/p15 and the malignant state.

Third, the Examiner alleges that the *in vitro* experiments of Liggett et al. are not indicative that a method of *in vivo* gene therapy as disclosed in the subject application and claimed is enabled. The Examiner refers, for example, to issues of efficient gene delivery and sustained gene expression, and states that the claimed methods are unpredictable with respect to achieving therapeutic levels of gene expression in the target cells. Applicants point out, however, that the claims require administration of a recited polynucleotide "locally at a site of" the target cells (see claims 1, 9, 18, 26 and 34). As such, it is submitted that the claimed methods are sufficiently analogous to the methods of Liggett et al., wherein the cells were contacted in culture, such that the skilled artisan would find Liggett et al. to provide confirmatory evidence that, as disclosed in the specification, a method as claimed would result in target cells at the site taking up the polynucleotide and expressing a 5'ALT/p15 or 5'ALT/p16 polypeptide. Further in this respect, it is noted that the claims do not require any particular level of efficacy, and the skilled artisan would have known that any level of efficacy can provide a therapeutic advantage to a patient suffering from a malignant neoplasm. Also, it is noted that issues such as determining an amount of an agent useful for a particular treatment are not issues related to patentability.

For the above reasons, it is submitted that one skilled in the art, viewing the specification and having knowledge of the art, would have known how to practice the claimed methods without undue experimentation. Accordingly, reconsideration and removal of the rejection of the claims under 35 U.S.C. 112, first paragraph, are respectfully requested.

In view of the amendments and the above remarks, it is submitted that the claims are in condition for allowance, and a notice to that effect respectfully is requested. Absent such a notice, it is requested that the finality of the Office Action be removed due to the newly raised rejection as discussed in Section B, above. The Examiner is invited to contact Applicants' undersigned representative if there are any questions relating to this application.

Please charge any additional fees, or make any credits, to Deposit Account No. 50-1355.

Respectfully submitted,

Date: April 10, 2003

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EXHIBIT A

Marked Version Showing Amendment to Claims

Claims 1, 9, 18, 26 and 34 were amended as follows:

1. (Four times amended) A method of treating a malignant cell proliferative disorder associated with decreased transcription of a 5'ALT polynucleotide comprising exon 2 of a p15 gene, the method comprising administering locally at a site of cells having or suspected of having the disorder a polynucleotide comprising SEQ ID NO:1 operatively linked to a polynucleotide comprising exon 2 of the p15 gene, the polynucleotide further operatively linked to an expression regulatory element, whereby expression of said polynucleotide restores transcription of the 5'ALT polynucleotide, thereby treating the malignant cell proliferative disorder.

9. (Four time amended) A method of treating a subject having a malignant cell proliferative disorder associated with decreased p16 expression due to methylation of a CpG island of a p16 gene in a cell, the method comprising administering locally at a site of malignant cells exhibiting decreased p16 expression in a subject with the disorder, a therapeutically effective amount of a polynucleotide comprising SEQ ID NO:1 operatively linked to exons 2 and 3 of the p16 gene, the polynucleotide further operatively linked to an expression regulatory element, whereby expression of the polynucleotide in the malignant cells in the subject is restored, thereby treating the subject.

18. (Twice amended) A method of suppressing proliferation of malignant cells characterized by decreased expression of a polynucleotide encoding a 5'ALT-p16^{INK4A} polypeptide, wherein said 5'ALT-p16^{INK4A} polypeptide has tumor suppressor activity, the method comprising administering locally at a site of the malignant cells a polynucleotide encoding a 5'ALT-p16^{INK4A} polypeptide, said polynucleotide comprising SEQ ID NO:1 operatively linked to exons 2 and 3 of a p16 gene, the polynucleotide further operatively linked to an expression regulatory element, wherein expression of the 5'ALT-p16^{INK4A} polypeptide suppresses

26. (Twice amended) A method of suppressing proliferation of malignant cells characterized by expression of a mutant 5'ALT-p16^{INK4A} polypeptide, wherein the mutant 5'ALT-p16^{INK4A} polypeptide has decreased tumor suppressor activity, the method comprising administering locally at a site of the malignant cells a polynucleotide encoding a 5'ALT-p16^{INK4A} polypeptide, said polynucleotide comprising SEQ ID NO:1 operatively linked to exons 2 and 3 of a p16 gene, the polynucleotide further operatively linked to an expression regulatory element, wherein expression of the 5'ALT-p16^{INK4A} polypeptide suppresses proliferation of the malignant cells.

34. (Amended) A method of treating a malignant cell proliferative disorder associated with decreased transcription of a 5'ALT polynucleotide comprising exons 2 and 3 of a p16 gene, the method comprising administering locally at a site of cells having or suspected of having the disorder a polynucleotide comprising SEQ ID NO:1 operatively linked to a polynucleotide comprising exons 2 and 3 of the p16 gene, the polynucleotide further operatively linked to an expression regulatory element, whereby expression of said polynucleotide restores transcription of the 5'ALT polynucleotide, thereby treating the malignant cell proliferative disorder.